

**BRIEFING**

**Artemether.** This standard was posted on the USP SALMOUS Standards Web page for review and public comment for more than 90 days. The MD-AA Expert Committee reviewed the following comments and approved the standard as an Authorized USP SALMOUS Standard.

**Comment:** It is proposed to correct the chemical name of Artemether. In addition, an editorial change to the name of artemether related compound A and B has also been made for consistency.

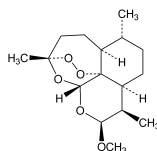
**Response:** Comment accepted.

The HPLC procedures used in the test for *Related compounds by HPLC* and in the *Assay* are based on analyses performed with the Purospher RP-18 (5- $\mu$ m) brand of L1 column. The typical retention times for artemether, artemether related compound A, and artemether related compound B are about 23, 7, and 15 minutes, respectively.

(MD-AA: L. Santos; B. Davani)      RTS—C50811; C66043

**Artemether**

v.1 Authorized February 1, 2009



$C_{16}H_{26}O_5$     298.37  
(3*R*,5*aS*,6*R*,8*aS*,9*R*,10*S*,12*R*,12*aR*)-Decahydro-10-methoxy-3,6,9-trimethyl-1,2-epoxy-12*H*-pyrano[4.3-*j*]-1,2-benzodioxepin [71963-77-4].

» Artemether contains not less than 98.0 percent and not more than 102.0 percent of  $C_{16}H_{26}O_5$ .

**Packaging and storage**—Preserve in well-closed, light-resistant containers. Store at room temperature.

**USP Reference standards** (11)—*USP Artemether RS*. *USP Artemether Related Compound A RS*. *USP Artemether Related Compound B RS*.

**Identification**—

**A:** *Infrared Absorption* (197K).

**B:** The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation*, as obtained in the *Assay*.

**Color of solution**—Transfer 1.00 g of Artemether to a 10-mL volumetric flask, dilute with acetone to volume, and mix. The absorbance of this solution, determined in 1-cm cells at 420 nm, with a suitable spectrophotometer and using acetone as the blank, is not greater than 0.10.

**Specific rotation** (781S):    between +166° and +173°, measured at 20°.

*Test solution:*    10 mg per mL, in dehydrated alcohol.

**Residue on ignition** (281):    not more than 0.1%.

**Heavy metals, Method II** (231):    0.001%.

**Related compounds by TLC**—

*Adsorbent:*    0.25-mm layer of chromatographic silica gel.

*Test solution*—Dissolve 100 mg of Artemether in 2 mL of acetone.

*Standard stock solution*—Dissolve suitable amounts of USP Artemether RS, USP Artemether Related Compound A RS, and USP Artemether Related Compound B RS in acetone to obtain a solution having a known concentration of about 1 mg of each per mL.

*Standard solutions*—Dilute an aliquot of *Standard stock solution* to obtain four *Standard solutions* having the following concentrations: 0.05 mg of each Standard per mL, 0.10 mg of each Standard per mL, 0.25 mg of each Standard per mL, and 0.50 mg of each Standard per mL.

*Application volume:*    2  $\mu$ L.

*Developing solvent system:*    a mixture of petroleum benzin, ethyl acetate, and glacial acetic acid (20 : 5 : 2.5).

*Procedure*—Proceed as directed for *Thin-Layer Chromatography* under *Chromatography* (621). Spray the plate with 20% sulfuric acid in methanol, and heat at 140° for about 10 minutes in a drying oven. Examine the plate under daylight. Estimate the percentage of all secondary spots observed in the chromatogram obtained from the *Test solution* by comparing each spot to the artemether spot in the chromatogram obtained from the chromatograms of the *Standard solutions*. The  $R_f$  values and limits of impurities are given in *Table 1*. [NOTE—Approximate  $R_f$  values for USP Artemether Related Compound A RS (dihydroartemisinin) and USP Artemether Related Compound B RS ( $\alpha$ -artemether) are 0.3 and 0.4, respectively.] Disregard any spots observed at the origins of the chromatograms. Disregard any spot corresponding to dihydroartemisinin and  $\alpha$ -artemether, because these impurities are quantified by the HPLC test.

**Table 1**

Compound	Approximate $R_f$	Limit (%)
Impurity 1	0.25	0.2
Impurity 2	0.35	0.2
Artemether	0.55	—
Any other individual impurity	—	0.1
Total impurities	—	0.4

**Related compounds by HPLC**—

*Mobile phase, System suitability solution, and Chromatographic system*—Proceed as directed in the *Assay*.

*Test solution*—Transfer about 100 mg of Artemether, accurately weighed, to a 10-mL volumetric flask, and add 7 mL of acetonitrile. Sonicate for 5 minutes, add about 2.5 mL of water, and sonicate again for 5 minutes. Dilute with water to volume.

*Procedure*—Inject a volume (about 20  $\mu$ L) of the *Test solution* into the chromatograph, and record the chromatogram. Identify the impurities, using the relative retention times specified in *Table 2*, and measure the peak responses.

**Table 2**

Compound	Relative Retention Time	Limit (%)
Artemether related compound A <sup>1</sup> (dihydroartemisinin)	0.3	0.2
Artemether related compound B <sup>2</sup> ( $\alpha$ -artemether)	0.7	0.2
Artemether	1.0	—
Any individual unknown impurities	—	0.1
Total unknown impurities	—	0.5

<sup>1</sup> (3*R*,5*aS*,6*R*,8*aS*,10*S*,12*R*,12*aR*)-Decahydro-10-hydroxy-3,6,9-trimethyl-3,12-epoxy-12*H*-pyrano[4.3-*j*]-1,2-benzodioxepin [ $C_{15}H_{25}O_5$ , 284.35]

<sup>2</sup> (3*R*,5*aS*,6*R*,8*aS*,10*R*,12*R*,12*aR*)-Decahydro-10-methoxy-3,6,9-trimethyl-3,12-epoxy-12*H*-pyrano[4.3-*j*]-1,2-benzodioxepin [ $C_{16}H_{26}O_5$ , 298.37]

## 2 / Artemether

Calculate the percentage of any individual impurity in the portion of Artemether taken by the formula:

$$100(r_i/r_s)$$

in which  $r_i$  is the peak area for each individual impurity, and  $r_s$  is the sum of all of the responses of all the peaks. Disregard any peak less than 0.05%.

**Assay—**

*Mobile phase*—Prepare a mixture of water and acetonitrile (6 : 4). Mix, degas, and make adjustments if necessary (see *System Suitability* under *Chromatography* (621)).

*Standard preparation*—Transfer an accurately weighed quantity of USP Artemether RS to a suitable volumetric flask, and dissolve in acetonitrile, using 70% of the final volume and sonicating if necessary. Dilute with water to volume, and mix to obtain a solution having a known concentration of about 10 mg of artemether per mL.

*Assay preparation*—Transfer about 100 mg of Artemether, accurately weighed, to a 10-mL volumetric flask, and add 7 mL of acetonitrile. Sonicate for 5 minutes, add about 2.5 mL of water, and sonicate again for 5 minutes. Dilute with water to volume.

*System suitability solution*—Transfer an accurately weighed quantity of USP Artemether RS, USP Artemether Related Compound A RS, and USP Artemether Related Compound B RS to a suitable volumetric flask, and dissolve in acetonitrile, using 70% of the final volume and sonicating if necessary. Dilute with water to volume, and

mix to obtain a solution having a concentration of about 10 mg per mL of artemether, 0.1 mg per mL of artemether related compound A, and 0.1 mg per mL of artemether related compound B.

*Chromatographic system* (see *Chromatography* (621))—The liquid chromatograph is equipped with a 210-nm detector and a 4.0-mm × 12.5-cm column that contains 5-μm packing L1. The flow rate is about 1 mL per minute. Chromatograph the *System suitability solution*, and record the peak responses as directed for *Procedure*: the resolution,  $R$ , between artemether and  $\alpha$ -artemether is not less than 2. Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure*: the relative standard deviation for replicate injections is not more than 2.0%.

*Procedure*—Separately inject equal volumes (about 20 μL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of  $C_{16}H_{26}O_5$  in the portion of Artemether taken by the formula:

$$100(C_s/C_u)(r_u/r_s)$$

in which  $C_s$  and  $C_u$  are the concentrations, in mg per mL, of artemether in the *Standard preparation* and the *Assay preparation*, respectively; and  $r_u$  and  $r_s$  are the peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively.